The Importance of Obtaining Information on the Specific Content of Tissue Enzymes Metabolizing Organophosphorus Pesticides, Prior to Determining V_{max}, K_m Values for Use in PBPK Models

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Physiological pharmacokinetic\pharmacodynamic models require V_{max}, K_m values for the metabolism of OPs by tissue enzymes. Current literature values cannot be easily used in OP PBPK models (i.e., parathion and chlorpyrifos) because standard methodologies were not used in their determination. In practically all cases, the investigators failed to determine the specific content of the enzymes of interest in tissues or tissue fractions (PON1 and P-450 isozymes) under investigation prior to use, by either spectral or immunochemical methods. The concentration of plasma PON1 (paraoxonase) may vary as much as 60 to 600 μg/ml, making it difficult to select proper enzyme-substrate concentrations for the determination of V_{max}, K_m. The same problem exists measuring P-450 activity using microsomal protein, when the specific content (pmoles of P-450, total or individual CYPs) in the microsomes is unknown. Rendic and Guengerich recently recommended individual CYPs (i.e, 1A2, 2B6, 2D6 and 3A4) be used to obtain V_{max}, K_m values in place of human whole liver microsomes. Mathematical equations are available for expressing individual CYP data (specific content and activity) in terms of native liver microsomes and using the data in PBPK models. Methods will be presented for obtaining V_{max}, K_m values for parathion and chlorpyrifos based on the specific content of PON1 and P-450 in plasma and liver microsomes.

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